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6-Substituted-5*H*-pyrrolo[2,3-*b*]pyrazines via palladium-catalyzed heteroannulation from *N*-(3-chloropyrazin-2-yl)-methanesulfonamide and alkynes

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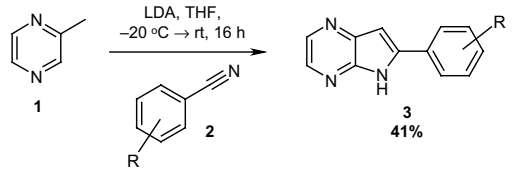
Abstract—We herein report the efficient and convenient synthesis of 6-substituted-5*H*-pyrrolo[2,3-*b*]pyrazines. The reaction is a palladium-catalyzed heteroannulation process followed by deprotection to yield the desired pyrrolo[2,3-*b*]pyrazine substrates. The reaction starts with readily accessible *N*-(3-chloropyrazin-2-yl)-methanesulfonamide and commercially available terminal alkynes and works with aryl- and alkylalkynes.

The indole ring structure has attracted the interest of organic chemists because of their wide range of biological activities.[1] Because of this interest there have been many elegant syntheses of this core structure and its many analogues using a variety of reaction conditions.[2] In addition to the indole core, the azaindoles have also received much synthetic interest due to their use as indole surrogates and as potential pharmaceutical agents.[3] However, even though the pyrrolo[2,3-*b*]pyrazines (diazaindoles) are starting to receive more attention from the pharmaceutical industry due to their interesting biological activities,[4] there has not been as much attention paid to their synthesis.[4a,5]

As part of our larger effort to discover and synthesize novel kinase inhibitors, we needed an efficient and viable pathway for the synthesis of 6-substituted-5*H*-pyrrolo[2,3-*b*]pyrazines.[6] Previously, the synthesis centered around the lithiation of methyl pyrazine **1**[5a–d,6] followed by reaction with an aryl cyanide **2** to yield the desired pyrrolo[2,3-*b*]pyrazine **3** in variable yields (Scheme 1). The yields varied depending on the nature of the R group on the arylnitrile (electron-donating groups worked well, but electron-withdrawing groups gave poor yields). The reaction also suffered from steric constraints as *ortho*-substituted arylnitriles gave poor yields. In addition, neither alkylnitriles nor nitriles with enolizable protons worked in this reaction.



Scheme 1. Synthesis of 2-substituted-4,7-diazaindoles lithiation reaction.

We next turned our attention to the two-step protocol of Sonogashira coupling[7] followed by base-induced cyclization (Scheme 2).[8] To this end, 2-amino-3-chloropyrazine **4**[9] was coupled with an appropriate terminal aryl alkyne under Sonogashira conditions to yield the desired 2-amino-3-alkynylpyrazine **6** (73% yield). Next, compound **6** was reacted under basic conditions to yield the desired pyrrolo[2,3-*b*]pyrazine **3** (60% yield) after intramolecular cyclization. The reaction sequence gave better yields, did not suffer from the reproducibility problems as did the previous approach, and the nature of the alkyne had less of an effect on the reaction success. However, the reaction sequence still was a two-step procedure with a needed isolation of the intermediate.

Keywords: 6-Substituted-5*H*-pyrrolo[2,3-*b*]pyrazine; Heteroannulation; Palladium; Cyclization.
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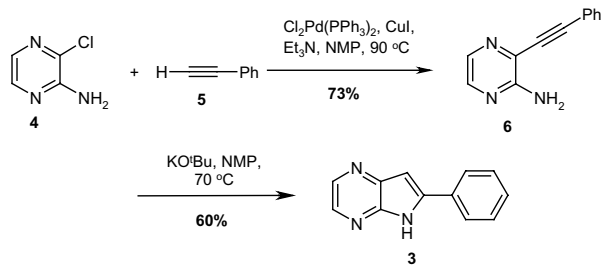


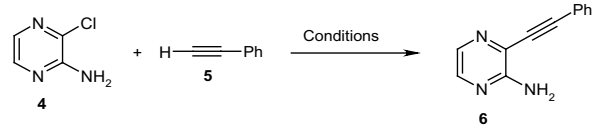
Scheme 2. Synthesis of 2-substituted-4,7-diazaindoles via two-step protocol of Sonogashira coupling followed by base-induced cyclization.

It is well known in the literature that indoles, azaindoles, and other pyrroloheterocycles can be formed by a palladium-catalyzed heteroannulation of terminal and internal alkynes using *ortho*-halogenaniline[10] or the heterocyclic equivalent.[11] This methodology is very powerful in that it allows for making the indole core from readily available materials in one step. The functional group tolerance is usually quite high and the product formed when reacting with terminal alkynes is exclusively the 6-substituted compound. However, much to our surprise after searching the literature, there were no examples of this reaction being applied to form the 6-substituted-5*H*-pyrrolo[2,3-*b*]pyrazine core structure. We herein report the efficient and convenient synthesis of 6-substituted-5*H*-pyrrolo[2,3-*b*]pyrazine via a palladium-catalyzed heteroannulation process followed by in situ deprotection to yield the desired diazindole substrates.

Our first attempts at this reaction were with the readily available 2-amino-3-chloropyrazine **4**[9] and a terminal alkyne **5** (Table 1). The reaction was investigated using the known literature protocols for the previously discussed heterocondensed pyrroles;[10,11] however, no cyclization product was detected. Depending on the reaction conditions, the substrate either only participated in the Sonogashira coupling (entries 1 and 3), or there was no reaction (entries 2 and 4). The reaction products obtained in entries 1 and 3 could be further cyclized in a separate step (base induced); however, we were only interested in the one-pot reaction. This result suggests that the nucleophilicity of the nitrogen group is not sufficient enough to permit cyclization.

Knowing there were several reports discussing the use of electron-withdrawing groups on the nitrogen to affect this transformation,[12] we turned our attention to such groups. After several attempts to synthesize the appropriate precursors, the sulfonyl group was determined to be the most viable.[13] We were anticipating the reaction to proceed with the final product being the cyclized *N*-sulfonylated material, as was obtained in the cited references. However, much to our delight, this compound[14] participated in the cyclization with concomitant deprotection of the sulfonyl group. The reported reaction conditions were evaluated (Table 2) and it was determined that $Cl_2Pd(dppf)$ was the optimum catalyst with the addition of LiCl and Na_2CO_3 in DMF at 100 °C (entry 8). It should be noted that a number of reaction conditions worked; however, it was decided that conditions of entry 8 would be pursued for further evaluation due to the shortened reaction times. As noted in the table, the reaction proceeds either in the presence (entries 1 and 2) or absence (entries 3 and 8) of copper(I) iodide.[15] The catalysts $Cl_2Pd(PPh_3)_2$ and $Cl_2Pd(dppf)$ (entries 1 and 2) were superior to the other catalysts under similar conditions. It was also determined that LiCl was the better halogen source resulting in higher yields and better

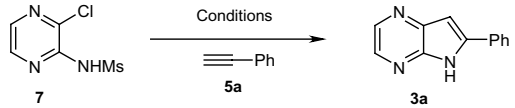
Table 1. Initial investigation of the heteroannulation cyclization with 2-amino-3-chloropyrazine



Entry	Conditions[a]	Product	Yield (%)
1	A	**6**	73
2	B	—	NR[b]
3	C	**6**	68[c]
4	D	—	NR[d]

[a] Conditions: A: $Pd(PPh_3)_4$, CuI, Et_3N, NMP, 90 °C, 5 h; B: $Pd(OAc)_2$, LiCl, P(*t*-Bu)$_3$, DMF, 100 °C, 14 h; C: $Cl_2Pd(dppf)$, CuI, 1,1,3,3-tetramethylquanidine (TMG), DMF, 100 °C, 18 h; D: $Cl_2Pd(dppf)$, LiCl, Na_2CO_3, DMF, 100 °C.
[b] SM recovered (67%).
[c] Includes ~10% of the cyclized material.
[d] SM recovered.

Table 2. Cyclization with 2-chloro-3-(*N*-methanesulfonamide)pyrazine; optimization of reaction conditions

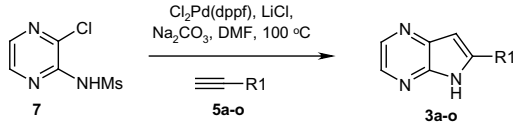


Entry	Conditions	Time (h)	Yield (%)
1	$Cl_2Pd(PPh_3)_2$, CuI, 1,1,3,3-tetramethylquanidine, DMF, 100 °C	8	46
2	$Cl_2Pd(dppf)$, CuI, 1,1,3,3-tetramethylquanidine, DMF, 100 °C	6	49
3	$Pd(OAc)_2$, Bu_4NCl, K_2CO_3, PPh_3, DMF, 100 °C	15	17
4	CuI, PPh_3, K_3PO_4, DMF, 100 °C	18	NR
5	$Cl_2Pd(MeCN)_2$, CuI, 1,1,3,3-tetramethylquanidine, DMF, 100 °C	7	Decomp.
6	$PdCl_2$, CuI, 1,1,3,3-tetramethylquanidine, DMF, 100 °C	8	Decomp.
7	$Pd(OAc)_2$, CuI, 1,1,3,3-tetramethylquanidine, DMF, 100 °C	6	Decomp.
8	$Cl_2Pd(dppf)$, LiCl, Na_2CO_3, DMF, 100 °C	3	63

reproducibility. This reaction works very well with the *o*-chloro derivative; all the previous examples used either the bromo- or iodo-derivative. This is an important aspect because the chloro derivative is the only compound that is readily available.

We set out to investigate the scope of this reaction with an emphasis on using aryl acetylenes that led to products that were either unattainable using the previous lithiation/cyclization protocol, or gave poor results.[16] As can be seen in Table 3, the reaction yields are good to very good for the overall three step, one-pot process (1. Coupling, 2. Cyclization, and 3. Deprotection). A variety of aryl acetylenes were investigated with all showing good yields. The reaction procedure tolerates both electron-donating groups (entries 14 and 15); and electron-withdrawing groups (entries 6–13), which did not participate (or were low yielding) in the previous route. The reaction also tolerates amino groups as well as ketones, *ortho*-substituents, and carboxylic acids. The reaction also proceeds with alkyl acetylenes (entries 2 and 16), which do not participate in the previous synthetic route.[17] A couple of drawbacks to this route are that: (1) reactions with silylalkynes only resulted in the isolation of the cyclized desilylated compounds (or a mixture of two compounds) under a number of isolation conditions, and (2) unprotected alcohols did not give any desired cyclization product.

Table 3. Synthesis of 6-substituted-5*H*-pyrrolo[2,3-*b*]pyrazines via palladium-catalyzed heteroannulation with terminal alkynes



7 5a-o 3a-o

Entry	R^1	Time (h)	Product	Yield (%)
1	Ph	3	**3a**	67
2	$-(CH_2)_3CH_3$	15	**3b**	52[a]
3	$-(CH_2)_2OH$	43	**3c**	[b]
4	TMS	15	**3d**	42[c]
5	TES	1	**3e**	36[d]
6	2-Trifluoromethylphenyl	1	**3f**	57
7	2-Pyridyl	2	**3g**	46
8	3-Acetylphenyl	1	**3h**	26[e]
9	4-Acetylphenyl	1	**3i**	21[e]
10	3-Acetylphenyl	7	**3h**	49[f]
11	4-Acetylphenyl	7	**3i**	52[f]
12	2-Chlorophenyl	1	**3j**	52
13	2-Fluorophenyl	1	**3k**	51
14	2-Methylphenyl	1.5	**3l**	57
15	3-Aminophenyl	2.5	**3m**	41
16	Cyclohexyl	16	**3n**	59
17	4-Benzoic acid	16	**3o**	41

[a] 85:15 Mixture of the cyclized desulfonylated and cyclized sulfonylated material (LC/MS, ^{1}H NMR).
[b] Decomposition.
[c] The desulfonylated, desilylated material was isolated (i.e., the unsubstituted diazaindole).
[d] The cyclized sulfonylated material was isolated.
[e] 2.8 equiv of starting ethynylacetophenone was used.
[f] 1.2 equiv of starting ethynylacetophenone was used.

In conclusion, the transition-metal catalyzed heteroannulation of alkynes with *N*-(3-chloropyrazin-2-yl)-methanesulfonamide provides a convenient and efficient new synthetic route to various 6-substituted-5*H*-pyrrolo[2,3-*b*]pyrazines. This technique provides an alternative to the previously reported procedures and allows for more structural diversity due to the greater functional group tolerance. The use of the aryl chloride is permitted for the first time in this reaction class. This reaction also allows for aryl, heteroaryl, and alkyl groups to be introduced at the 6-position. Further elaboration of this reaction methodology is currently ongoing in our labs and will be reported in due course.

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13. Compound **7** was obtained in 66% yield from the reaction of 2,3-dichloropyrazine with methanesulfonamide in DMSO at 115 °C. Attempts to make the acetamide or carbamate derivatives failed.
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16. Representative example: Compound **7** (146.1 mg; 0.7036 mmol), phenylacetylene (232 μL; 1.043 mmol), $Cl_2Pd(dppf)$ (27.1 mg; 0.0332 mmol), LiCl (30.4 mg; 0.717 mmol), and Na_2CO_3 (136.8 mg; 1.291 mmol) were dissolved in DMF (4.0 mL) and then a stream of N_2 was passed through for 10 min. The reaction mixture was then heated at 100 °C for 3 h, cooled to rt, and diluted with H_2O. The mixture was extracted with EtOAc and then the organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (10 g pre-packed column from ISCO, 50% heptane–EtOAc eluent) to yield 118.5 mg (0.4715 mmol; 67%) of 6-phenyl-5*H*-pyrrolo[2,3-*b*]pyrazine **3a** as a yellow solid. HPLC (SYNERGI 2U HYDRO-RP 20X4.0MM COL, water (0.1% trifluoroacetic acid)/acetonitrile (0.1% trifluoroacetic acid) = 10/90 → 90/10): R_f = 2.45 min. $C_{12}H_9N_3$ (195.23) MS (ESI) 196 (M+H). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 12.5 (s, 1H), 8.36 (d, 1H, J = 2.5 Hz), 8.21 (d, 1H, J = 2.6 Hz), 8.02 (d, 2H, J = 7.2 Hz), 7.51 (t, 2H, J = 7.1 Hz), 7.42 (t, 1H, J = 7.2 Hz), 7.15 (d, 1H, J = 1.8 Hz).
17. The alkylnitrile (entry 3) gave a mixture of cyclized desulfonylated and cyclized sulfonylated material with the major product being the cyclized desulfonylated compound.